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(54) **ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF**

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None

See application file for complete search history.

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(57) **ABSTRACT**

An antibiotic product is comprised of at least three dosages forms, each of which has a different release profile, with the C_{max} for the antibiotic product being reached in less than about twelve hours after the initial release of antibiotic. In one embodiment, there is a delayed release dosage form, as well as two or more delayed sustained release dosage forms, with each of the dosage forms having a different release profile, wherein each reaches a C_{max} at different times.

19 Claims, No Drawings

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ANTIBIOTIC PRODUCT, USE AND FORMULATION THEREOF

This application is a continuation of U.S. application Ser. No. 10/917,059 filed Aug. 12, 2004 (now U.S. Pat. No. 8,062,672), which claims the priority of U.S. Provisional Application Ser. No. 60/494,454 filed on Aug. 12, 2003, the disclosures of which are hereby incorporated by reference in their entireties.

This invention relates to an antibiotic product, as well as the use and formulation thereof.

A wide variety of antibiotics have been used, and will be used, in order to combat bacterial infection. In general, such antibiotics can be administered by a repeated dosing of immediate release dosage forms, which results in poor compliance or as a controlled release formulation (slow release) at higher administered doses. The present invention is directed to providing for an improved antibiotic product.

In accordance with one aspect of the present invention, there is provided an antibiotic pharmaceutical product which is comprised of at least two, preferably at least three, antibiotic dosage forms. Such dosage forms are formulated so that each of the dosage forms has a different release profile.

In a particularly preferred embodiment, there are at least two, preferably at least three dosage forms, each of which has a different release profile and the release profile of each of the dosage forms is such that the first and second dosage forms each start release of the antibiotic contained therein at about the same time, and the third dosage form starts release of the antibiotic contained therein at a time after the second dosage form starts release of antibiotic contained therein.

In another particularly preferred embodiment, there are at least two, preferably at least three dosage forms, each of which has a different release profile and the release profile of each of the dosage forms is such that the dosage forms each start release of the antibiotic contained therein at different times after administration of the antibiotic product.

Thus, in accordance with an aspect of the present invention, there is provided a single or unitary antibiotic product that has contained therein at least two, preferably at least three antibiotic dosage forms, each of which has a different release profile, whereby the antibiotic contained in at least two of such dosage forms is released at different times.

In general neither of the second or third dosage forms starts release of antibiotic contained therein before the first dosage form starts release of antibiotic contained therein.

More particularly, in one aspect, the antibiotic product contains at least three dosage forms, the first of which is a delayed release dosage form, the second of which is a delayed release sustained release dosage form, and the third of which is a delayed release sustained release dosage form, with the second dosage form initiating release at about the same time as the first dosage form or at a time after the first dosage form (the initiation of sustained release is delayed for a period of time after initiation of release from the first dosage form), with the third dosage form initiating release after release is initiated from both the first and second dosage forms.

In accordance with a further aspect of the invention, the antibiotic product may be comprised of at least four different dosage forms, at least three of which starts to release the antibiotic contained therein at different times after administration of the antibiotic product.

The antibiotic product generally does not include more than five dosage forms with different release times.

In accordance with a preferred embodiment, the antibiotic product has an overall release profile such that when administered the maximum serum concentration of the total antibiotic released from the product is reached in less than twelve hours, preferably in less than eleven hours after initiation of release of antibiotic from the first dosage form. In an embodiment, the maximum serum concentration of the total antibiotic released from the antibiotic product is achieved no earlier than four hours after initiation of release of antibiotic from the first dosage form.

In accordance with one preferred embodiment of the invention, there are at least three dosage forms. The first of the at least three dosage forms is a delayed release dosage form whereby initiation of release of the antibiotic therefrom is delayed after administration of the antibiotic product. The second and third of the at least three dosage forms are each delayed sustained release dosage forms. Additionally, initiation of release of the antibiotic from the third sustained release dosage form is delayed until after initiation of release from the second, however, when release is initiated the second and third dosage forms release antibiotic as sustained release dosage forms. The delay of initiation of release of each of the sustained release dosage forms, may be accomplished for example by using a pH sensitive or a non-pH sensitive enteric coating, depending on the type of antibiotic product, whereby the sustained release of the antibiotic from the second and third dosage form is delayed with the second dosage form initiating release at about the same time or at a time after initiation of release of antibiotic from the first dosage form. More particularly, the antibiotic released from the second of the at least two dosage forms achieves a C_{max} (maximum serum concentration in the serum) at a time after the antibiotic released from the first of the at least three dosage forms achieves a C_{max} in the serum, and the antibiotic released from the third dosage form achieves a C_{max} in the serum after the C_{max} of antibiotic released from the second dosage form.

In one embodiment the first and second of the at least two dosage forms initiate their respective delayed and delayed sustained releases of antibiotic at about the same time.

In one embodiment the initiation of the sustained release of antibiotic from the second of the at least two dosage forms is delayed until after the initiation of release of antibiotic from the first dosage form.

In all embodiments comprising three or more dosage forms, the initiation of the sustained release of antibiotic from the third dosage form is delayed until after the sustained release of antibiotic is initiated from the second dosage form.

In one embodiment, the second of the at least two dosage forms initiates release of the antibiotic contained therein at least one hour after the first dosage form, with the initiation of the release therefrom generally occurring no more than six hours after initiation of release of antibiotic from the first dosage form of the at least three dosage forms.

In general, the first dosage form produces a C_{max} for the antibiotic released therefrom within from about 0.5 to about 2 hours after initiation of release of antibiotic, with the second dosage form of the at least three dosage forms producing a C_{max} for the antibiotic released therefrom in no more than about four hours after initiation of release of antibiotic from the first dosage form. In general, the C_{max} for such second dosage form is achieved no earlier than two hours after initiation of release of antibiotic from the first dosage form; however, it is possible within the scope of the invention to achieve C_{max} in a shorter period of time.

As hereinabove indicated, the antibiotic product may contain at least three or at least four or more different dosage forms. For example, if the antibiotic product includes a third dosage form, the antibiotic released therefrom reaches a C_{max} at a time later than the C_{max} is achieved for the antibiotic

released from each of the first and second dosage forms. In a preferred embodiment, release of antibiotic from the third dosage form is started after initiation of release of antibiotic from both the first dosage form and the second dosage form. In one embodiment, C_{max} for antibiotic release from the third dosage form is achieved within eight hours after initiation of release of antibiotic from the first dosage form.

In another embodiment, the antibiotic product contains at least four dosage forms, with each of the at least four dosage forms having different release profiles, whereby the antibiotic released from each of the at least four different dosage forms achieves a C_{max} at a different time.

As hereinabove indicated, in a preferred embodiment, irrespective of whether the antibiotic contains at least two or at least three or at least four different dosage forms each with a different release profile, C_{max} for all the antibiotic released from the antibiotic product is achieved in less than twelve hours, and more generally is achieved in less than eleven hours after initiation of release of antibiotic from the first is initiated.

In a preferred embodiment, the antibiotic product is a once a day product, whereby after administration of the antibiotic product, no further product is administered during the day; i.e., the preferred regimen is that the product is administered only once over a twenty-four hour period. Thus, in accordance with the present invention, there is a single administration of an antibiotic product with the antibiotic being released in a manner such that overall antibiotic release is effected with different release profiles in a manner such that the overall C_{max} for the antibiotic product is reached in less than twelve hours after initiation of release of antibiotic. The term single administration means that the total antibiotic administered over a twenty-four hour period is administered at the same time, which can be a single tablet or capsule or two or more thereof, provided that they are administered at essentially the same time.

Applicant has found that a single dosage antibiotic product comprised of at least three antibiotic dosage forms each having a different release profile is an improvement over a single dosage antibiotic product comprised of an antibiotic dosage form having a single release profile. Each of the dosage forms of antibiotic in a pharmaceutically acceptable carrier may have one or more antibiotics and each of the dosage forms may have the same antibiotic or different antibiotics.

It is to be understood that when it is disclosed herein that a dosage form initiates release after another dosage form, such terminology means that the dosage form is designed and is intended to produce such later initiated release. It is known in the art, however, notwithstanding such design and intent, some "leakage" of antibiotic may occur. Such "leakage" is not "release" as used herein.

If at least four dosage forms are used, the fourth of the at least four dosage forms may be a sustained release dosage form or a delayed release dosage form. If the fourth dosage form is a sustained release dosage form, even though C_{max} of the fourth dosage form of the at least four dosage forms is reached after the C_{max} of each of the other dosage forms is reached, antibiotic release from such fourth dosage form may be initiated prior to or after release from the second or third dosage form.

The antibiotic product of the present invention, as hereinabove described, may be formulated for administration by a variety of routes of administration. For example, the antibiotic product may be formulated in a way that is suitable for topical administration; administration in the eye or the ear; rectal or vaginal administration; as nose drops; by inhalation; as an injectable; or for oral administration. In a preferred embodiment, the antibiotic product is formulated in a manner such that it is suitable for oral administration.

For example, in formulating the antibiotic product for topical administration, such as by application to the skin, the at least two different dosage forms, each of which contains an antibiotic, may be formulated for topical administration by including such dosage forms in an oil-in-water emulsion, or a water-in-oil emulsion. In such a formulation, the delayed release dosage form is in the continuous phase, and the delayed sustained release dosage form is in a discontinuous phase. The formulation may also be produced in a manner for delivery of three dosage forms as hereinabove described. For example, there may be provided an oil-in-water-in-oil emulsion, with oil being a continuous phase that contains the delayed release component, water dispersed in the oil containing a first delayed sustained release dosage form, and oil dispersed in the water containing a third sustained release dosage form.

It is also within the scope of the invention to provide an antibiotic product in the form of a patch, which includes antibiotic dosage forms having different release profiles, as hereinabove described.

In addition, the antibiotic product may be formulated for use in the eye or ear or nose, for example, as a liquid emulsion. For example, the dosage form may be coated with a hydrophobic polymer whereby a dosage form is in the oil phase of the emulsion, and a dosage form may be coated with hydrophilic polymer, whereby a dosage form is in the water phase of the emulsion.

Furthermore, the antibiotic product with at least three different dosage forms with different release profiles may be formulated for rectal or vaginal administration, as known in the art. This may take the form of a cream or emulsion, or other dissolvable dosage form similar to those used for topical administration.

As a further embodiment, the antibiotic product may be formulated for use in inhalation therapy by coating the particles and micronizing the particles for inhalation.

In a preferred embodiment, the antibiotic product is formulated in a manner suitable for oral administration. Thus, for example, for oral administration, each of the dosage forms may be used as a pellet or a particle, with a pellet or particle then being formed into a unitary pharmaceutical product, for example, in a capsule, or embedded in a tablet, or suspended in a liquid for oral administration.

Alternatively, in formulating an oral delivery system, each of the dosage forms of the product may be formulated as a tablet, with each of the tablets being put into a capsule to produce a unitary antibiotic product. Thus, for example, antibiotic products may include a first dosage form in the form of a tablet that is a delayed release tablet, and may also include two or more additional tablets, each of which provides for a delayed sustained release of the antibiotic, as hereinabove described, whereby the C_{max} of the antibiotic released from each of the tablets is reached at different times, with the C_{max} of the total antibiotic released from the antibiotic product being achieved in less than twelve hours after initial release of antibiotic.

The formulation of an antibiotic product including at least three dosage forms with different release profiles for different routes of administration is deemed to be within the skill of the art from the teachings herein. As known in the art, with respect to sustained release, the time of release can be controlled by the concentration of antibiotics in the coating and/or the thickness of the coating.

In accordance with the present invention, each of the dosage forms contains the same antibiotic; however, each of the dosage forms may contain more than one antibiotic.

Immediate Release Component

An immediate release component may be initially produced and then coated to produce the delayed release dosage forms used in the present invention.

An immediate release component is used in formulating the delayed release dosage form and can be a mixture of ingredients that breaks down quickly after administration to release the antibiotic. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other three components.

The materials to be added to the antibiotics for the immediate release component can be, but are not limited to, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylatedchitosan, cross-linked chitosan, cross-linked hydroxymethyl chitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives (Carbopol, Eudragit, etc.), polyethylene glycols, such as low molecular weight PEGs (PEG2000-10000) and high molecular weight PEGs (Polyox) with molecular weights above 20,000 daltons.

It may be useful to have these materials present in the range of 1.0 to 60% (W/W). More preferably these materials are present in the range of 3-40%. Most preferably these materials are present in the range of 5-20% so that the drug loading may be kept high and the overall dosage form size is minimized.

In addition, it may be useful to have other ingredients in this system to aid in the dissolution of the drug, or the breakdown of the component after ingestion or administration. These ingredients can be surfactants, such as sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monostearate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, caprylocaproyl macrogol-8-glycerides, one of the non-ionic surfactants such as the Pluronic line of surfactants, or any other material with surface active properties, or any combination of the above. The material may also be a disentegrant or superdisentegrant known to those in the art such as coscarmellose sodium, cross linked PVP, and others.

These materials may be present in the rate of 0.05-15% (W/W).

The Non-pH Sensitive Delayed Release Component

The components in this composition are the same as the immediate release unit, but with additional polymers integrated into the composition, or as coatings over the pellet or granule. Several methods to affect a delayed release with non pH dependent polymers are known to those skilled in the art. These include soluble or erodible bather systems, enzymatically degraded barrier systems, rupturable coating systems, and plugged capsule systems among others. These systems have been thoroughly described in the literature (see "A Review of Pulsatile Drug Delivery" by Bussemer and Bodmeier in the Winter 2001 issue of American Pharmaceutical Review) and formulations and methods for their manufacture are hereby incorporated by reference.

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit RS) cellulose acetate, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component. Preferably the materials are present in an amount just enough to provide the desired in vivo lag time and T_{max}.

The pH Sensitive (Enteric) Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate pthalate, Eudragit L, Eudragit S, Eudragit FS, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W) or more. Preferably the materials are present in an amount just enough to provide the desired in vivo lag time and T_{max}.

Sustained Release Component

The components in this composition are the same as the immediate release component, but with additional polymers integrated into the composition, or as coatings over the pellet or granule.

The kind of materials useful for this purpose can be, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, methylcellulose, nitrocellulose, Eudragit RS, and Eudragit RL, Carbopol, or polyethylene glycols with molecular weights in excess of 8,000 daltons.

These materials can be present in concentrations from 4-20% (W/W). Preferably the amounts are just enough to provide the desired in vivo release profile.

When it is desired to delay initiation of release of the sustained release dosage form, an appropriate coating may be used to delay initiation of the sustained release, such as a pH sensitive or a non-pH sensitive coating.

The Non-pH Sensitive Coating for Sustained Release Dosage Form

Materials that can be used to obtain a delay in release suitable for this component of the invention can be, but are not limited to, polyethylene glycol (PEG) with molecular weight above 4,000 daltons (Carbowax, Polyox), waxes such as white wax or bees wax, paraffin, acrylic acid derivatives (Eudragit RS), cellulose acetate, and ethylcellulose.

Typically these materials can be present in the range of 0.5-25% (W/W) of this component. Preferably the materials are present in an amount just enough to provide the desired in vivo lag time and T_{max}.

The pH Sensitive Coating for Sustained Release Dosage Form

The kind of materials useful for this purpose can be, but are not limited to, cellulose acetate pthalate, Eudragit L, Eudragit S, Eudragit FS, and other pthalate salts of cellulose derivatives.

These materials can be present in concentrations from 4-20% (W/W) or more. Preferably the materials are present in an amount just enough to provide the desired in vivo lag time and T_{max}.

As hereinabove indicated, the units comprising the antibiotic composition of the present invention can be in the form of discrete pellets or particles contained in the capsule, or particles embedded in a tablet or suspended in a liquid suspension.

The antibiotic composition of the present invention may be administered, for example, by any of the following routes of administration; sublingual, transmucosal, transdermal,

parenteral, etc., and preferably is administered orally. The composition includes a therapeutically effective amount of the antibiotic, which amount will vary with the antibiotic to be used, the disease or infection to be treated, and the number of times that the composition is to be delivered in a day. The composition is administered to a host in an amount effective for treating a bacterial infection.

This system will be especially useful in extending the practical therapeutic activity for antibiotics with elimination half lives of less than 20 hours and more particularly with elimination half-lives of less than 12 hours, and will be particularly useful for those drugs with half-lives of 2-10 hours. The following are examples of some antibiotics with half-lives of about 1 to 12 hours: Cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephacelor, cephprozil, cephadrine, cefamandole, cefonicid, ceforanide, cefuroxime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftaxidime, ceftibuten, ceftizoxime, ceftriaxone, cefepime, cefmetazole, cefotetan, cefoxitin, loracarbef, imipenem, erythromycin (and erythromycin salts such as estolate, ethylsuccinate, gluceptate, lactobionate, stearate), azithromycin, clarithromycoin, dirithromycin, troleanomycin, penicillin V, penicillin salts, and complexes, methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, amoxicillin, amoxicillin and clavulanate potassium, ampicillin, bacampicillin, carbenicillin indanyl sodium (and other salts of carbenicillin) mezlocillin, piperacillin, piperacillin and taxobactam, ticarcillin, ticarcillin and clavulanate potassium, clindamycin, vancomycin, novobiocin, aminosalicylic acid, capreomycin, cycloserine, ethambutol HCl and other salts, ethionamide, and isoniazid, ciprofloxacin, levofloxacin, lomefloxacin, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, sulfacytine, sulfamerazine, sulfamethazine, sulfamethixole, sulfasalazine, sulfisoxazole, sulfapyrizine, sulfadiazine, sulfinethoxazole, sulfapyridine, metronidazole, methenamine, fosfomycin, nitrofurantoin, trimethoprim, clofazimine, co-triamoxazole, pentamidine, and trimetrexate.

The invention will be further described with respect to the following examples; however, the scope of the invention is not limited thereby. All percentages in this specification, unless otherwise specified, are by weight.

EXAMPLES

I. Immediate Release Component

Formulate the composition by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a dry blend. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum over or forced-air oven. The product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into a capsule or sachet with a suitable filler.

	Ingredient	Conc. (% W/W)
Example 1:	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Povidone	10
	Croscarmellose sodium	5
Example 2:	Amoxicillin	55% (W/W)
	Microcrystalline cellulose	25
	Povidone	10
	Croscarmellose sodium	10

-continued

	Ingredient	Conc. (% W/W)
Example 3:	Amoxicillin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 4:	Amoxicillin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 5:	Amoxicillin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 6:	Clarithromycin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 7:	Clarithromycin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5
Example 8:	Clarithromycin	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 9:	Clarithromycin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 10:	Ciprofloxacin	65% (W/W)
	Microcrystalline cellulose	20
	Hydroxypropylcellulose	10
	Croscarmellose sodium	5
Example 11:	Ciprofloxacin	75% (W/W)
	Microcrystalline cellulose	15
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5
Example 12:	Ciprofloxacin	75% (W/W)
	Polyethylene glycol 4000	10
	Polytheylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 13:	Cirpofloxacin	75% (W/W)
	Polyethylene glycol 8000	20
	Polyvinylpyrrolidone	5
Example 14:	Ceftibuten	75% (W/W)
	Polyethylene glycol 4000	10
	Polyethylene glycol 2000	10
	Hydroxypropylcellulose	5
Example 15:	Ceftibuten	75% (W/W)
	Polyethylene Glycol 4000	20
	Polyvinylpyrrolidone	5

II. Non-pH Sensitive Delayed Release Component

Any of the methods described in "A Review of Pulsatile Drug Delivery" by Bussemer and Bodmeier in the Winter 2001 issue of American Pharmaceutical Review may be utilized to make the pH independent delayed release component described. Examples 16 and 17 utilize an organic acid layer underneath a layer of Eudragit RS to result in a rapid increase in the permeability of the Eudragit film after a set amount of time depending on the permeability and thickness of the film thus allowing the inner core to release through the Eudragit membrane. Example 18 utilizes a core with a highly swellable polymer that ruptures the insoluble coating membrane after a certain amount of time determined by the permeability, plasticity and thickness of the external cellulose acetate membrane. The coatings are applied to the core via methods such as wurster column coating in a fluid bed processor as known to those skilled in the art.

Additionally, this component may be formed as in example 19. In this example the component is prepared by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed

granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven.

After the component is allowed to cool, the product may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into a capsule with a suitable encapsulator.

	Ingredient	Conc. (% W/W)
Example 16:	Core from Example 4	65% (W/W)
	Citric Acid	10
	Eudragit RS Polymer	20
	Talc	4
	TEC	1
Example 17:	Core from Example 9	75% (W/W)
	Citric Acid	10
	Eudragit RS Polymer	10
	Talc	4
	TEC	1
Example 18:	Core from Example 1	93% (W/W)
	Cellulose Acetate	6.75
	PEG 400	0.25
Example 19:	Ciprofloxacin	70% (W/W)
	Polyox	20
	Hydroxypropylcellulose	5
	Croscarmellose sodium	5

II. Enteric Delayed Release Component

Examples 20-27 utilize film coating techniques commonly known to those skilled in the art to create the enteric release component by layering of such enteric polymers onto an active core. In general the steps involve first making a coating dispersion or solution in organic or aqueous solvent. Second, the coating is applied at the proper conditions to produce an acceptably uniform film. This is done in a suitable coating apparatus such as a pan coater or a fluid bed wurster column coater. Optionally the product may be further cured if necessary.

To create a matrix type enteric component, formulate the ingredients of examples 28-32 by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool.

The product produced by either manner may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into capsules using a suitable capsule filler such as a MG2 Futura.

	Ingredient	Conc. (% W/W)
Example 20:	Core from Example 1	65% (W/W)
	Cellulose Acetate Pthalate	30
	TEC	5
Example 21:	Core from Example 5	75% (W/W)
	Cellulose Acetate Pthalate	20
	Triacetin	5
Example 22:	Core from Example 1	65% (W/W)
	Eudragil L	25
	Talc	8
	TEC	2
Example 23:	Core from Example 1	65% (W/W)
	Eudragit FS	28

-continued

	Ingredient	Conc. (% W/W)
	Talc	5
	TEC	2
Example 24:	Core from Example 1	65% (W/W)
	Eudragit S	28
	Talc	5
	TEC	2
Example 25:	Core from Example 7	75% (W/W)
	Eudragit L	20
	Talc	3.5
	TEC	1.5
Example 26:	Core from Example 11	60% (W/W)
	Eudragit L	35
	Talc	4
	TEC	1
Example 27:	Core from Example 15	65% (W/W)
	Cellulose Acetate Pthalate	32.5
	TEC	2.5
Example 28:	Amoxicillin	75% (W/W)
	Microcrystalline Cellulose	5
	Hydroxypropylcellulose pthalate	20
Example 29:	Amoxicillin	60% (W/W)
	Lactose	10
	Eudgragit L 30D	30
Example 30:	Ciprofloxacin	70% (W/W)
	Polyethylene glycol 4000	10
	Cellulose acetate pthalate	20
Example 31:	Clarithromycin	60% (W/W)
	Polyethylene glycol 2000	10
	Lactose	20
	Eudragit L 30D	10
Example 32:	Ceftibuten	70% (W/W)
	Microcrystalline cellulose	20
	Cellulose acetate pthalate	10

IV. Sustained Release Component

Examples 33-38 utilize film coating techniques commonly known to those skilled in the art to create the sustained release component by layering of such sustained release polymers onto an active core. In general the steps involve first making a coating dispersion or solution in organic or aqueous solvent. Second, the coating is applied at the proper conditions to produce an acceptably uniform film. This is done in a suitable coating apparatus such as a pan coater or a fluid bed wurster column coater. Optionally the product may be further cured if necessary. Curing studies are recommended with sustained release membranes.

To create a matrix type sustained release component, formulate the ingredients of example 39-42 by mixing the ingredients in a suitable pharmaceutical mixer or granulator such as a planetary mixer, high-shear granulator, fluid bed granulator, or extruder, in the presence of water or other solvent, or in a hot melt process. If water or other solvent was used, dry the blend in a suitable pharmaceutical drier, such as a vacuum oven or forced-air oven. Allow the product to cool.

The product produced by either manner may be sieved or granulated, and compressed using a suitable tablet press, such as a rotary tablet press, or filled into capsules using a suitable capsule filler such as a MG2 Futura.

	Ingredient	Conc. (% W/W)
Example 33:	Core from Example 1	75% (W/W)
	Ethylcellulose	20
	HPC	5
Example 34:	Core from Example 5	80% (W/W)
	Eudragit RS	10

-continued

	Ingredient	Conc. (% W/W)
	Eudragit RL	5
	Talc	3
	TEC	2
Example 35:	Core from Example 5	90% (W/W)
	Ethylcellulose	9
	Triacetin	1
Example 36:	Core from Example 7	90% (W/W)
	Surelease	10
Example 37:	Core from Example 11	85% (W/W)
	Kollicoat SR	10
	TBC	5
Example 38:	Core from Example 15	80% (W/W)
	Polyethylene glycol 8000	5
	Eudgragit RS 30D	15
Example 39:	Amoxicillin	75% (W/W)
	Hydroxyethylcellulose	10
	Polyethylene glycol 4000	10
	Hydroxypropylcellulose	5
Example 40:	Ciprofloxacin	75% (W/W)
	Lactose	10
	Povidone (PVP)	10
	Polyethylene glycol 2000	5
Example 41:	Clarithromycin	75% (W/W)
	Polyethylene glycol 4000	10
	Povidone (PVP)	10
	Hydroxypropylcellulose	5
Example 42:	Ceftibuten	75% (W/W)
	Lactose	15
	Polyethylene glycol 4000	5
	Polyvinylpyrrolidone	5

V. Sustained Release Dosage Form with Coating to Delay Initiation of Sustained Release

Delaying the initiation of the sustained release of antibiotic in the present invention is achieved by either coating the immediate release component bead with a sustained release coating and then subsequently applying an enteric coating or non-pH sensitive delayed release coating to that coated bead, or alternatively the sustained release matrix component bead may be coated with an enteric coating or non-pH sensitive delayed release coating.

Coatings can be applied to either the sustained release coated beads or the sustained release matrix beads to form a product which pulses the therapeutical agent in a desired environment or location of the GI tract.

V A. The following examples describe the detailed preparation of the sustained-release coating materials to be applied to the immediate release beads from section I of the examples, resulting in a sustained release component of the invention.

Example 43

Eudragit RS Example—Organic Coating

Component Part A	Percentage (%)
Eudragit RS-100	6.0
Triethyl Citrate	1.0
Talc	0.5
Acetone	92.5

Step 1. Dissolve Eudragit in Acetone.
Step 2. Mix TEC and talc in a separate container with some Acetone.
Step 3. Add step 2 to Step 1, and allow to mix for 20 minutes before spraying.

Example 44

Surelease™ Example—Aqueous Coating

Component Part A	Percentage (%)
Surelease	90
Purified Water	10.0

Step 1. Mix surelease and water for 30 minutes before spraying.

Directions for application of the sustained release coating to the beads:

Charge a wurster column equipped fluid bed with the beads to be coated. Spray the coating onto the beads at a rate and temperature known to those skilled in the art of bead coating so as to efficiently coat the beads to give a weight gain of between 4 and 20%. Dry the beads to the specified level of coating solvent for optimum handling and stability. Cure the beads for additional congealing of the sustained release film if required.

V B. The following are examples of the pH sensitive, or enteric release, coating that can be used to optionally delay the onset of action of any or all of the second, third, or additional dosage forms.

The composition of the aqueous Eudragit L30D-55 dispersion to be applied to the immediate release components that have been treated with the above-described sustained release coatings, or to the sustained-matrix pellets is provided below in Example 45.

Example 45

Eudragite® L 30 D-55 Aqueous Coating Dispersion

Component	Percentage (%)
Eudragit ® L 30 D-55	55.0
Triethyl Citrate	1.6
Talc	8.0
Purified Water	37.4
Solids Content	25.5
Polymer Content	15.9

Preparation Procedure for an Eudragit® L 30 D-55 Aqueous Dispersion
Step 1 Suspend triethyl citrate and talc in deionized water.
Step 2 The TEC/talc suspension is then homogenized using a PowerGen 700 high shear mixer.
Step 3 Add the TEC/talc suspension slowly to the Eudragit® L 30 D-55 latex dispersion while stirring.
Step 4 Allow the coating dispersion to stir for one hour prior to application onto the matrix pellets.

Example 46

Preparation of an Eudragit® S 100 Aqueous Coating Dispersion Dispersion Formulation

The composition of the aqueous Eudragit® S 100 dispersion applied to the matrix pellets is provided below:

Eudragit® S 100 Aqueous Coating Dispersion

Component	Percentage (%)
Part A	
Eudragit ® S 100	12.0
1N Ammonium Hydroxide	6.1
Triethyl Citrate	6.0
Purified Water	65.9
Part B	
Talc	2.0
Purified Water	8.0
Solid Content	20.0
Polymer Content	12.0

Preparation Procedure for an Eudragit® S 100 Aqueous Dispersion

Part I:

(i) Dispense Eudragit® S 100 powder in deionized water with stirring.

(ii) Add ammonium hydroxide solution drop-wise into the dispersion with stirring.

(iii) Allow the partially neutralized dispersion to stir for 60 minutes.

(iv) Add triethyl citrate drop-wise into the dispersion with stirring. Stir for about 2 hours prior to the addition of Part 13.

Part II:

(i) Disperse talc in the required amount of water

(ii) Homogenize the dispersion using a PowerGen 700D high shear mixer.

(iii) Part B is then added slowly to the polymer dispersion in Part A with a mild stirring.

Coating Conditions for the Application of Aqueous Coating Dispersions

The following coating parameters were used to coat matrix pellets with each of the Eudragit® L 30 D-55 and Eudragit® S 100 aqueous film coating.

Coating Equipment	STREA 1 ™ Table Top Laboratory Fluid Bed Coater
Spray nozzle diameter	1.0 mm
Material Charge	300 gram
Inlet Air Temperature	40 to 45° C.
Outlet Air Temperature	30 to 33° C.
Atomization Air Pressure	1.8 Bar
Pump Rate	2 gram per minute

(i) Coat matrix pellets with L30 D-55 dispersion such that you apply 12% coat weight gain to the pellets.

(ii) Coat matrix pellets with S100 dispersion such that you apply 20% coat weight gain to the pellets.

V. C. The following examples describe the detailed preparation of the non pH sensitive coating materials to be used to optionally delay the onset of action of any or all of the second, third, or additional dosage forms.

Example 47

Rupturable Film

Component Part A	Percentage (%)
Cellulose Acetate 398-10	6.0
PEG 400	1.5
Acetone	92.5

Step 1. Dissolve cellulose acetate in Acetone.

Step 2. Add TEC to Step 1, and allow to mix for 20 minutes.

Directions for application of the sustained release coating to the beads:

Charge a wurster column equipped fluid bed with the beads to be coated. The beads must contain a component which will swell rapidly upon exposure to moisture. Beads containing croscarmellose sodium in Section I are good candidates as are beads with swellable hydrophilic polymers from Section IV. Spray the coating onto the beads at a rate and temperature known to those skilled in the art of bead coating so as to efficiently coat the beads to give a weight gain of between 4 and 20%. Dry the beads to the specified level of coating solvent for optimum handling and stability.

Coating Conditions for the Application of the Rupturable Film Coating.

The following coating parameters were used to coat matrix mini tablets from example 39 with the rupturable film coating. A 2.5% weight gain provided the desired lag time.

Coating Equipment	Vector LDCS Coating System with 1.3 L pan
Spray nozzle diameter	0.8 mm
Material Charge	800 grams
Inlet Air Temperature	40 to 45° C.
Outlet Air Temperature	18 to 23° C.
Atomization Air Pressure	25 psi
Pump Rate	6 grams per minute

The enteric coatings and non-pH sensitive coatings as described above can be applied to either a sustained release matrix bead as in examples 33-42, or to the immediate release component beads that have been previously treated with a sustained release coating, to thereby provide a sustained release bead with a delayed onset of action. In addition, the enteric coating or non-pH sensitive coating can be applied to the immediate release component bead directly to provide delayed onset of action.

VI. Final Composition

After all of the individual components are manufactured the final dosage form is assembled and may take the shape of a tablet, capsule or sachet. Preferably the final dosage form takes the shape of a capsule or tablet. Most preferably the final dosage form is a tablet.

The various dosage forms will be combined in the final dosage form in a ratio such that the Cmax is achieved in less than twelve hours after initiation of release of antibiotic and the product provides once a day coverage of anti-infective agent. Preferably the first, second, and third dosage forms provides 20-70%, 10-70%, and 10-70% of the total dosage form, respectively. More preferably the ratio of first, second

and third dosage forms are in the range of 25-66%, 15-60%, and 15-60% of the total dosage form respectively. Most preferably the ratio of the first, second and third dosage forms are in the range of 33-60%, 25-50%, and 25-50%, respectively.

The present invention is particularly advantageous in that there is provided an antibiotic product which provides an improvement over twice a day administration of the antibiotic and an improvement over a once a day administration of the antibiotic.

Numerous modifications and variations of the present invention are possible in light of the above teachings, and therefore, within the scope of the appended claims the invention may be practiced otherwise than as particularly described.

What is claimed is:

1. A once-a-day antibiotic product comprising:

first, second, and third antibiotic dosage forms, each of said antibiotic dosage forms comprising at least one antibiotic and a pharmaceutically acceptable carrier,

said first antibiotic dosage form being a delayed release dosage form,

said second and third antibiotic dosage forms being delayed sustained release dosage forms comprising:

a sustained release component and a delayed release component,

wherein the sustained release component comprises nitrocellulose, an acrylic acid derivative or a polyethylene glycol with a molecular weight above 8,000 daltons,

wherein the delayed release component comprises a polyethylene glycol with molecular weight above 4,000 daltons, a wax, a paraffin, cellulose acetate, cellulose acetate pthalate, or anionic polymers of methacrylic acid and methacrylates with a COOH group

wherein said second dosage form initiates release of antibiotic at about the same time as said first dosage form initiates release of antibiotic and Cmax of the total antibiotic released from said antibiotic product is achieved in less than about 12 hours from initial release of antibiotic and said once-a-day antibiotic product contains the total dosage of the at least one antibiotic for a twenty-four hour period.

2. The product of claim **1**, wherein the Cmax for the product is reached no earlier than four hours after initial release of antibiotic.

3. The product of claim **1**, wherein the antibiotic released from the first dosage form reaches a Cmax within from about 0.5 hours to about 2 hours after initial release of antibiotic.

4. The product of claim **1**, wherein the product is an oral dosage form.

5. The product of claim **1**, wherein the antibiotic released from the second dosage form reaches a Cmax after Cmax is reached for the antibiotic released from the first dosage form.

6. The product of claim **1**, wherein the antibiotic released from the third dosage form reaches a Cmax after Cmax is reached for the antibiotic released from the second dosage form.

7. The product of claim **1**, wherein the first dosage form contains about 20-70% of the total dosage of antibiotic, the second dosage form contains about 10-70% of the total dosage of antibiotic, and the third dosage form contains about 10-70% of the total dosage of antibiotic.

8. The product of claim **1**, wherein the first dosage form contains about 25-66% of the total dosage of antibiotic, the second dosage form contains about 15-60% of the total dosage of antibiotic, and the third dosage form contains about 15-60% of the total dosage of antibiotic.

9. The product of claim **1**, wherein the first dosage form contains about 33-60% of the total dosage of antibiotic, the second dosage form contains about 25-50% of the total dosage of antibiotic, and the third dosage form contains about 25-50% of the total dosage of antibiotic.

10. The product of claim **1**, further comprising a fourth antibiotic dosage form, said fourth antibiotic dosage form being either a sustained or a delayed release dosage form and comprising at least one antibiotic and a pharmaceutically acceptable carrier and wherein said at least one antibiotic released from said fourth antibiotic dosage form reaches a Cmax after Cmax is achieved for antibiotic released from each of said first, second, and third dosage forms.

11. The product of claim **10**, wherein the Cmax for the product is reached no earlier than four hours after initial release of antibiotic.

12. The product of **10**, wherein the antibiotic released from the first dosage form reaches a Cmax within from about 0.5 hours to about 2 hours after initial release of antibiotic.

13. The product of **10**, wherein the antibiotic released from the second dosage form reaches a Cmax in no more than about 4 hours after initial release of antibiotic.

14. The product of **10**, wherein the product is an oral dosage form.

15. The product of **10**, wherein the antibiotic released from the second dosage form reaches a Cmax after Cmax is reached for the antibiotic released from the first dosage form.

16. The product of **10**, wherein the antibiotic released from the third dosage form reaches a Cmax after Cmax is reached for the antibiotic released from the second dosage form.

17. A process for treating a bacterial infection in a host comprising: administering to a host the antibiotic product of claim **1**, once-a-day.

18. The product of claim **1**, wherein the acrylic acid derivative is a copolymer of acrylate and methacrylates with quarternary ammonium groups.

19. The product of claim **1**, wherein the antibiotic is amoxicillin.

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